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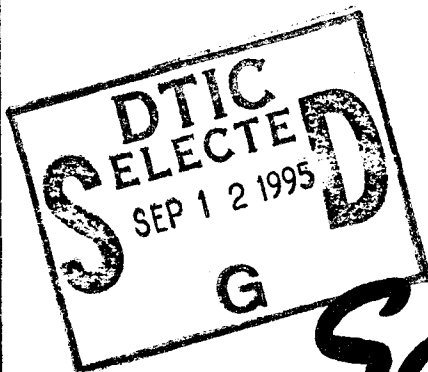
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# *School of* **AVIATION MEDICINE**

NEUROHISTOLOGICAL INVESTIGATIONS ON GENERAL  
OXYGEN DEFICIENCY OF THE BRAIN

II. The Behavior of Astrocytes After Acute and Subacute Death

PROJECT NUMBER 21-23-004  
REPORT NUMBER 2

## PROJECT REPORT

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**NEUROHISTOLOGICAL INVESTIGATIONS ON GENERAL  
OXYGEN DEFICIENCY OF THE BRAIN**

**II. The Behavior of Astrocytes After Acute and Subacute Death**

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**USAF SCHOOL OF AVIATION MEDICINE  
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## THE BEHAVIOR OF ASTROCYTES AFTER ACUTE AND SUBACUTE DEATH

It is well known that in fresh brain softenings, clasmotodendrosis develops within the focus, whereas the astrocytes surrounding the focus maintain their structure. Figure 1 shows such a phenomenon in a softening due to an embolism that had occurred 5 hours before death. At first, such a finding does not seem very peculiar. The clasmotodendrosis might be explained as a consequence of a necrobiosis caused by the arrest of the circulation. Obviously, a prolonged duration of the anoxic state is the decisive factor for its development. The conservation of the cells beyond the focus would indicate that, premortally, these cells had not been subjected to such anoxia, and that no "postmortem" or "autolytic" changes had yet developed. Strictly speaking, however, at the instant of the individual's death an anoxic condition had arisen also for them.

If we presume, as we do with the cells within the focus, that they continue to live in this condition for a certain length of time, it might be expected that between death and fixation of the brain—in this case, a period of 20 hours—there would have developed at least slight necrobiotic phenomena. But this is not so. Consequently, one must deduce that the *duration* of the anoxic phase is not the only factor responsible for the different behavior of the cells.

Is it possible that the temperature plays an important role in this connection? After the instant of the individual's death, the temperature conditions were the same for both the focus and the surrounding tissue. Since the corpse had not been kept in a particularly cool place, it can be presumed that the temperature of the brain, after a possible slight rise (postmortem heat congestion), had gradually fallen to about room temperature within the 20 hours. The focal tissue, however, immediately after becoming anoxic, had remained within the range of body temperature for an additional 5 hours prior to death. This likewise does not seem to be the reason for the difference in the

cell structure. With such slight difference in time one should detect at least signs of a beginning degeneration of the cells outside the focus.

These areas, however, differed from each other also in the rate of transition from normal oxygen supply to the state of anoxia. With the pertinent artery occluded, the focal cells suddenly became deprived of the oxygen supply, causing the acute onset of the stroke. For the remaining brain tissue, there was a subacute transition resulting from the agonal, gradually increasing deterioration of respiration and circulation. *Could the difference in this transition furnish the explanation of our problem?*

In order to study this problem an investigation was made of brains following acute and subacute death. It was assumed that it makes no difference to the astrocytes whether they are stricken by acute anoxia caused by an embolus or by sudden arrest of the heart. By acute death is meant one preceded by severe hypoxia lasting for seconds and minutes; by subacute death, one following severe hypoxia lasting for hours.

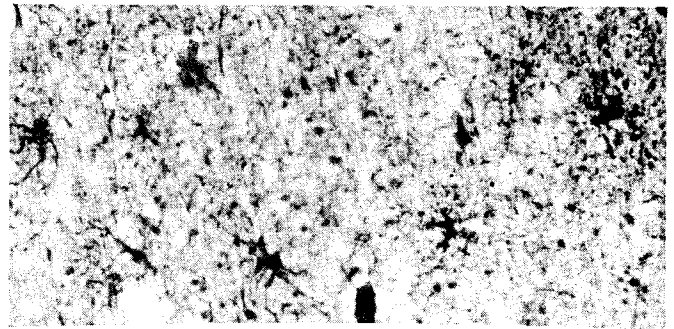


FIGURE 1

Border area of a fresh softening caused by an embolism 5 hours prior to death. The right side of the picture shows a clasmotodendrosis of the astrocytes within the focus. The arrow points to the borderline of the focus. The astrocytes outside the focus did not lose their structure. Fixation of the brain 20 hours after death.

The criterion selected to determine the degree of hypoxia was the loss of consciousness, provided it was due to hypoxia; in all other cases, e.g., trauma, it was the onset of respiratory disturbances. The cessation of cardiac activity served as criterion for the onset of death. Unless an individual dies instantly, one cannot determine definitely the moment of the last heart beat. It is a well-known fact that the heart may go on beating for more than 10 minutes. In the present study only those cases have been chosen that had no organic disease prior to death. All observations not made by the author were checked subsequently whenever possible with the nurses or rescue teams to verify statements concerning the onset of death and the preceding symptoms. The same holds true for the time the autopsies were made and for the way the corpses were stored. When possible, sections from all parts of the brain were examined histologically and stained by methods common in neuropathology. For the presentation of astrocytes, the original Cajal method was used. Although this method reveals only the general structure of the cells, it was considered sufficient for the purpose at hand. This method proved uniformly successful when used with fresh material. The astrocytes were selected for this investigation because they manifest swelling and disintegration most impressively.

Since the findings show a relatively narrow range of variation, the cases will be summarized in two groups.

## DESCRIPTION OF CASES

### 1. Acute death.

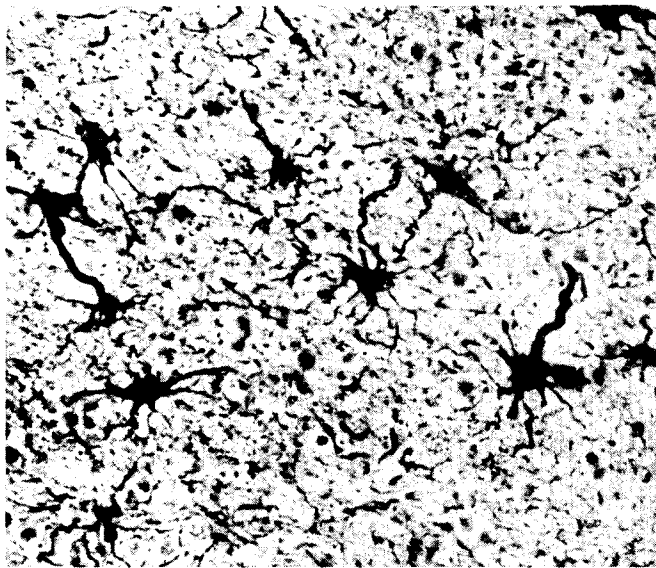
This group consists of a series of 18 casualties that occurred in a certain type of aircraft accident, the nose-over. Since the causative factor of death and the anatomical findings were the same in all 18 cases, this group is considered first. The ages of the victims ranged between 20 and 30 years. Prior to death all of them had been in good health. When the aircraft nosed over, the pilots—while in a head-down position—were jackknifed with such violence that they died of suffocation within 10 minutes. All of them showed severe cyanosis of the head. Most of these accidents occurred during the winter months, so the bodies cooled off relatively fast. The span of time between death and the fixation of the brain, i.e., the phase of postmortem anoxia, ranged from 18 to 46 hours. Despite this difference in time, the findings made on the astrocytes were practically the same in all cases. In each case, parts of all the important brain regions down to the medulla oblongata were examined.

The following findings were universal: In the cerebral cortex, the protoplasmic processes of the astrocytes were

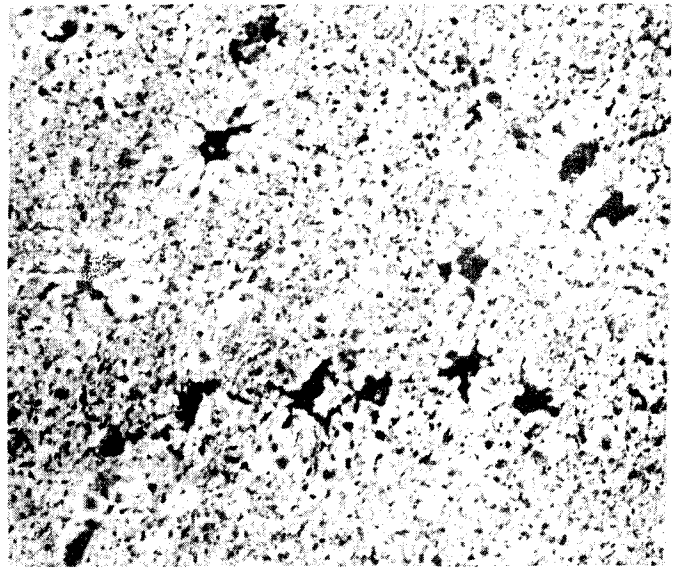
degenerated more or less distinctly. In several cases, however, they were well preserved and showed no peculiarities. In the immediate subcortical layer of the white matter, about as wide as the U-fibers, the astrocytes showed no degeneration, but generally a mild swelling which made their processes appear very clearly. Often they seemed irregular and shaggy; in many cases, the sucker feet pulling on the vessels were markedly swollen. In the cell body perinuclear transparencies of the protoplasm and vacuolar formations were occasionally recognized (fig. 2a). Next to this zone, which was usually only a few cells wide, the astrocytes were likewise swollen; yet the first signs of clasmatodendrosis were already visible on one or more processes (fig. 2b). The transparent regions in the cell bodies were often more distinct. Proceeding more deeply into the white matter, fully developed clasmatodendrosis was encountered. The original form of the astrocytes was recognized only by the arrangement of the fragments of the cell processes. Finally, in the center of the white matter of the hemispheres, especially in the internal capsule, destruction was complete. Here and there, agglomerations of protoplasmic particles were to be seen, indicating the former position of the cell bodies. At first sight this picture was suggestive of the formation of artifacts (fig. 2c). In this picture can be seen the extent to which the cell body may be permeated with "vacuoles," as well as typical agglomerations of protoplasm around a vessel, i.e., the remnants of the normally fine sucker feet and of the membrana gliae limitans. In the basal ganglia the astrocytes of the corpus striatum usually underwent the same changes as did those of the cortex; often they degenerated into fine granules. In the thalamus, however, they frequently maintained their structure. But even if they had disintegrated, the astrocytes of the pallidum and of the central gray matter around the third ventricle preserved their forms. In many cases they did not even show a swelling. Such cells are shown in figure 2d. It is plainly visible that the processes of the astrocytes are embracing a ganglion cell of the pallidum. This picture is especially impressive, inasmuch as it was taken from the immediate vicinity of the cells shown in figure 2c. In the pons, degeneration associated with swelling was a common finding in its basilar part. In the tegmentum the cells were mostly intact, though occasionally swollen. In the cerebellar white matter, swelling and degeneration were found, whereas the astrocytes in the granular-cell layer of the cortex had generally retained their form. In the medulla oblongata the astrocytes showed, as a rule, surprisingly good resistance. Degeneration and swelling were occasionally observed in the region of the thicker pathways. The glia marginalis above the cerebral cortex often showed neither degeneration nor swelling. This was also true of the subependymal glia.

In view of the uniformity of age, type of accident, cause and acuteness of death, and histological findings, this series of cases is comparable to an experimental series. The degeneration of the astrocytes showed the same pattern of distribution in all cases. It is similar to that found in cases of symptomatic brain swelling. For convenience it will be referred to as a *generalized*, in contrast to a *localized*, clasmatodendrosis.

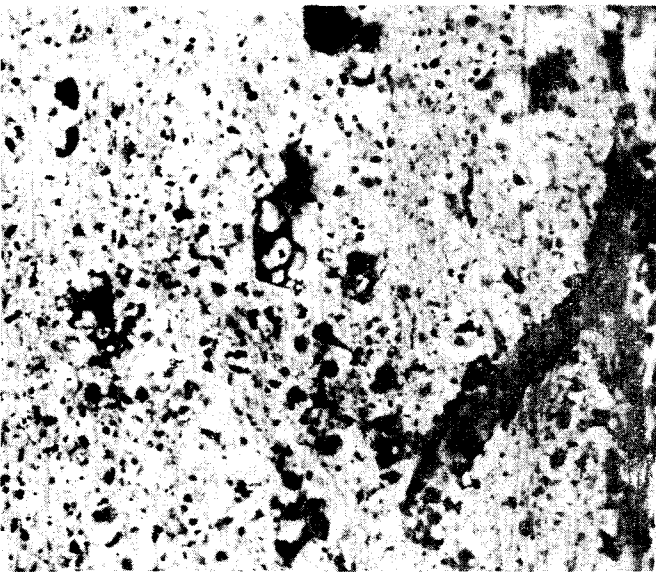
Four other cases that likewise died of acute suffocation by entombment—two in sand and two in snow—showed essentially the same changes. Two cases that died of



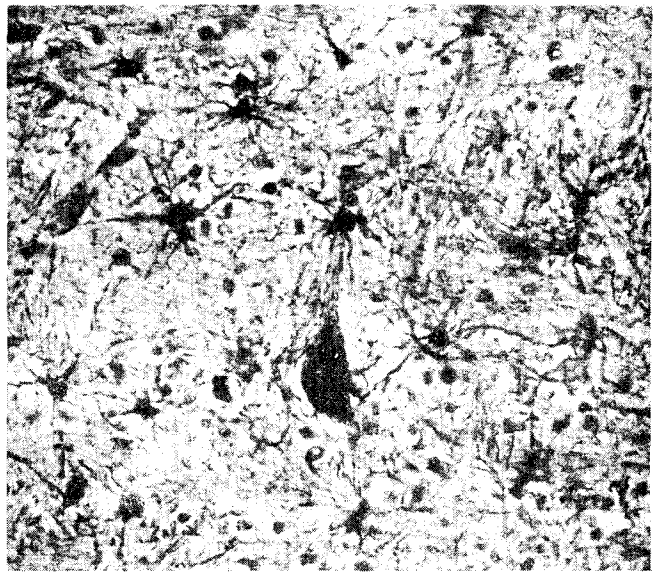
(a)



(b)



(c)



(d)

## FIGURE 2

Astrocytes in acute death due to suffocation.

- a. Acute swelling with thickening of the "sucker feet" in the subcortical zone of the white matter.
- b. Clasmotodendrosis of acutely swollen cells in the outer zone of the deeper white matter.
- c. Total destruction combined with vacuolization in the internal capsule.
- d. Preservation of the cell structure in the pallidum of the same case as in figure 1c.

suffocation in snow were especially interesting inasmuch as the brains had probably cooled off faster than any of the others, and were finally frozen. Although they were permeated with very fine pores caused by ice crystals, clasmotodendrosis was clearly visible. Consequently, it must have developed relatively soon after death.

For the sake of comparison, cases that had committed suicide by hanging were examined. Four such cases, all adolescents, demonstrated the same findings, varying within a very narrow range. The autopsies had been performed 21 to 36 hours after death; the bodies had been kept cool.

In connection with all these cases the question may be raised as to whether oxygen deficiency was the sole factor that had led to the changes in the astrocytes, or whether an excessive accumulation of carbon dioxide in the blood, and consequently in the tissues, might have played a role. The answer to this question became apparent through the examination of a higher altitude death in which such an overloading with carbon dioxide did not take place. So far as is known this is the first case of high altitude death that has been investigated for the behavior of the astrocytes. The autopsy was performed 24 hours after death; the body had been kept cool. The findings are reproduced in figures 3a and b. In figure 3a, the astrocytes are situated in the subcortical zone of the cerebrum. Their form is barely maintained; they have a shaggy appearance, and one of the cells shows a distinct swelling of the body and perinuclear vacuole-like transparencies. The cells in figure 3b are located in the deeper white matter of the cerebral hemisphere and show a complete destruction of the cell processes. Hence, an excessive accumulation of carbon dioxide could not have been responsible for the development of the acute swelling as well as of the clasmotodendrosis.

Furthermore, cases were investigated in which death had occurred instantaneously by extremely severe traumatic lacerations of the internal organs involving rupture of the heart. Altogether 10 cases were examined; the span of time between death and fixation of the brain ranged from 15 to 48 hours, and the bodies had been stored in a cool place. All 10 cases disclosed a clasmotodendrosis with acute swelling of varying extent distributed throughout the brain as described above. Figure 4 shows a section from the zone between putamen and palidum. The astrocytes of the pallidum have maintained their structure, whereas the finer astrocytes of the putamen are almost completely destroyed.

Considering these findings, the appearance of clasmotodendrosis in all cases of acute death (as by coronary occlusion, fatal pulmonary embolism, or bleeding) was no longer surprising. Altogether, 9 of these cases were studied, the fixation time ranging from 12 to 26 hours with the usual cooling of the bodies.

All the aforementioned cases passed away within a period of approximately 30 minutes. The following 4 cases died after a severe hypoxic phase of about 30 to 60 minutes' duration. Two of them had bled to death and the other 2 died of acute alcoholic intoxication.

The first case of this group, the victim of an explosion, had suffered an injury to the upper part of the right thoracic cavity. Some branches of the arteria subclavia were lacerated causing a hemothorax of about 2,500 cc. in the right cavity and collapse of the right lung. Further-

more, contusions had inflicted hemorrhages to the upper lobe of the left lung. A few minutes after the injury the victim lost consciousness and, with intensifying pallor, passed away about 30 minutes later. The autopsy was performed 40 hours after death. The corpse had been kept in

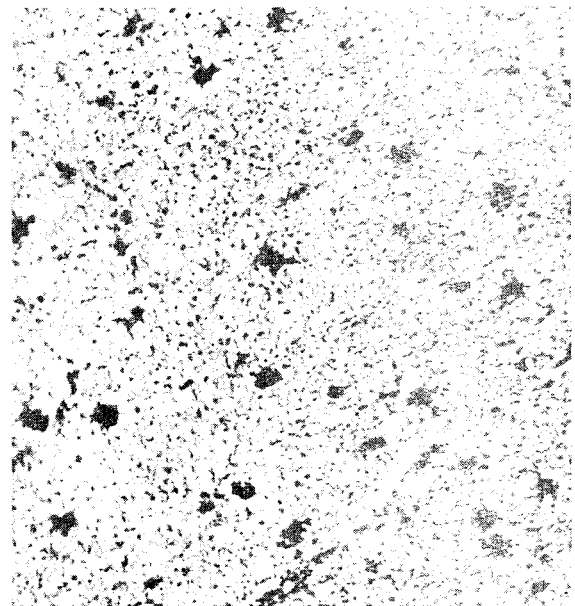
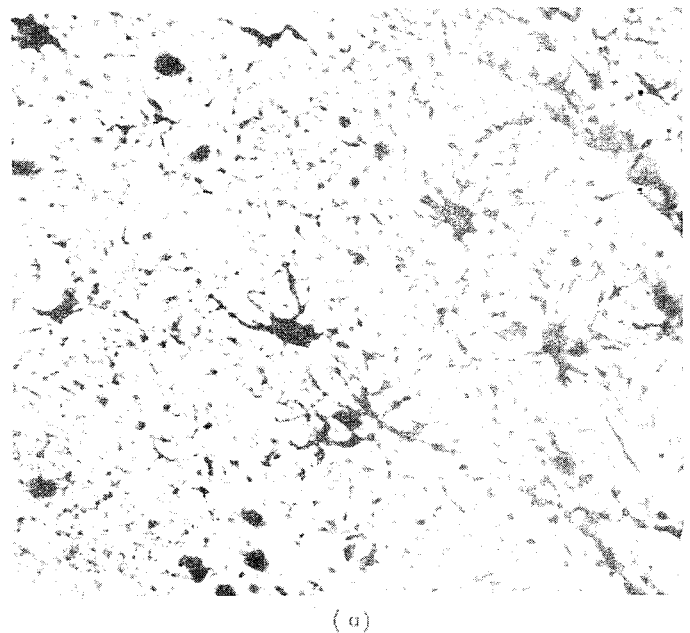
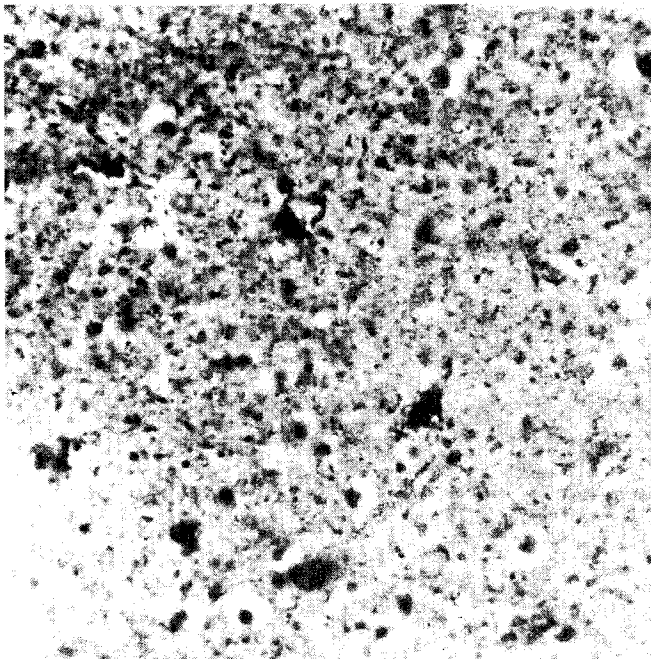


FIGURE 3

- Astrocytes in a case of acute high-altitude death.
- Acute swelling combined with vacuolization in the subcortical zone of the white matter.
  - Clasmotodendrosis of all astrocytes in the deeper, white matter.

**FIGURE 4**

Borderlike zone between putamen (left) and pallidum (right) in a case of acute death due to severe trauma. The astrocytes of the putamen are almost completely destroyed; the astrocytes of the pallidum have maintained their structure.

**FIGURE 5**

Clasmotodendrosis with vacuolization in the white matter of a case who died after severe hypoxia lasting about 30 minutes. Signs of acute swelling are missing.

a cool place. The astrocytes of the white matter had degenerated. There was, however, no such acute swelling as seen in the former cases. In some places they showed a vacuolization (fig. 5). Most astrocytes of the cortex had also degenerated without noticeable swelling. The cells of the subcortical region and of the brain stem again had kept their form.

The second case, the victim of an accident, had suffered an injury to the right side of the neck. The wound extended into the oral cavity; branches of the external carotid artery were lacerated. Owing to the bleeding into the oral cavity he had aspirated large quantities of blood. At first, he was conscious for a few minutes; then he became drowsy and finally unconscious. The respiration deteriorated, and after about 40 minutes in this condition he died. The autopsy was performed 24 hours after death; the corpse had not been kept in a very cool place. Also, in this case a clasmotodendrosis was found in the white matter of the hemispheres, but there was no acute swelling. In some places there were only fine granules of the cell processes and hardly any traces of the cell bodies. The astrocytes of the cortex were maintained almost exclusively; likewise, those of the immediate cortical vicinity, of the striatum, thalamus, hypothalamus, pallidum, pons, and medulla oblongata, with some exceptions in their thicker pathways.

The two other cases concerned men who had consumed large amounts of cognac or rum within a relatively short time. Very soon, both fell into a narcotic state which the other members of the party had at first taken for a sound sleep. In the one man, about 30 to 40 minutes before his death, a considerable deterioration of respiration set in with increasing cyanosis; in the other, the same occurred about 45 to 60 minutes before death. Both died of respiratory and circulatory paralysis.

The autopsy was made after 7 hours in the one case, and after 15 hours in the other. The bodies had cooled off slowly since they had remained clothed for a considerable length of time. The case with the shorter hypoxic phase revealed a degeneration of the astrocytes in the white matter without any noticeable swelling; some cells of the cortex had degenerated, whereas the subcortical astrocytes were maintained, likewise without any distinct swelling. The other case revealed only a few signs of clasmotodendrosis in the deeper regions of the white matter, whereas the cells of the other brain sections, including the cortex, subcortical area, basal ganglia, and pons were maintained; part of them appeared to have shrunk (fig. 6).

## 2. Subacute death.

The findings were quite different in cases of subacute death. These casualties likewise involved younger people who had no organic disease before the accident occurred.

**Case 1.** A man, 23 years old, who fell on his face, suffered injury to the tongue and fracture of the nasal bone. In the initial phase of grogginess, he lost relatively much blood and, moreover, aspirated blood. A little later, he was able to consult a physician. During the examination, he was slightly drowsy. About one hour before his death he became unconscious and respiration deteriorated. He died 2 hours and 20 minutes after the accident. According to the postmortem finding, death was caused by subacute suffocation as a consequence of excessive



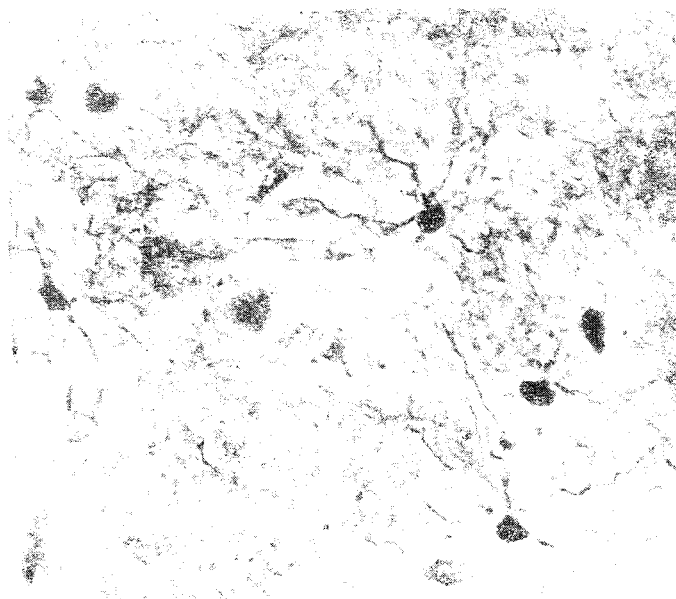


FIGURE 6

Astrocytes of the outer zone of the white matter in a case of alcohol intoxication with severe hypoxia lasting for 45-60 minutes prior to death. The cells appear to have shrunk.

blood aspiration with an extremely severe pulmonary edema. No traumatic injury of the brain was found. The autopsy was performed 24 hours after death. The corpse had been kept cool. The histological examination of the astrocytes did not indicate any acute swelling or clasmotodendrosis in either the gray or the white matter. Figure 7 shows astrocytes of the white matter.

**Case 2.** When jumping off a diving board, the individual suffered a fracture of the larynx by colliding with another swimmer. Immediately he suffered from severe dyspnea which was aggravated by the development of a glottic edema, leading to loss of consciousness. This severe hypoxic state lasted about an hour. In the summer heat the corpse had cooled very slowly; the autopsy was performed about 20 hours after death. Neither in the gray nor in the white matter did the histological examination of the astrocytes reveal an acute swelling or even a beginning clasmotodendrosis. On the contrary, most cell bodies were small and the cell processes especially fine. Occasionally, these processes showed fine loops that looked like tiny knots (fig. 8). Such peculiar formations were found in a number of other cases. Whether this was a pathological change or a result of fixation could not be determined. At any rate, in this problem it was important merely to know that the cells had maintained their form and showed neither acute swelling nor degeneration.

**Case 3.** A woman who had fallen into deep water was rescued shortly before drowning. She was unconscious and had a livid-blue discoloration of the skin and signs of extensive water aspiration. Despite medication, dyspnea increased and the heart weakened. She died 2 hours after the accident. The postmortem examination disclosed

water aspiration and severe pulmonary edema. dilation of both cardiac ventricles, passive congestion of the internal organs. The fixation of the brain was carried out 48 hours after death and after usual cooling of the corpse. Preparations from all parts of the brain down to the medulla oblongata showed no swelling or degeneration of the astrocytes in either the white or the gray matter.

In 3 further similar cases in which the terminal hypoxia had lasted from 1 to 2 hours, the bodies had been kept in cool places, and the postmortem examination had been performed 18 to 26 hours after death, the astrocytes in the gray and in the white matter had likewise been preserved.

Furthermore, 4 cases of subacute carbon monoxide poisoning were investigated where death had occurred between 5 and 10 hours after the onset of poisoning. The cooling of the corpses was relatively slow and the postmortem examinations were conducted 33 to 48 hours after death. Here, too, the astrocytes yielded no signs of degeneration.

To this group may be added 8 further cases that had suffered head injuries and survived for periods of from 4 to 20 hours. They had in common a gradual deterioration of respiration and circulation over a prolonged span of time; besides, none of them showed any infection. After usual cooling of the bodies in a refrigerator the autopsies were performed 12 to 28 hours after death. In these cases the intention was to investigate at the same time the problem of whether or not the percussion of the brain mass during the impact might have had any influence on the astrocytes. In general cytology, it is known that the cytoplasm reacts to mechanical stimuli by liquefaction, a process that is called *thixotropy* (Peterfi). Hallervorden used this principle to explain the origin of the cortical contusion foci and their peculiar wedge shape. It was

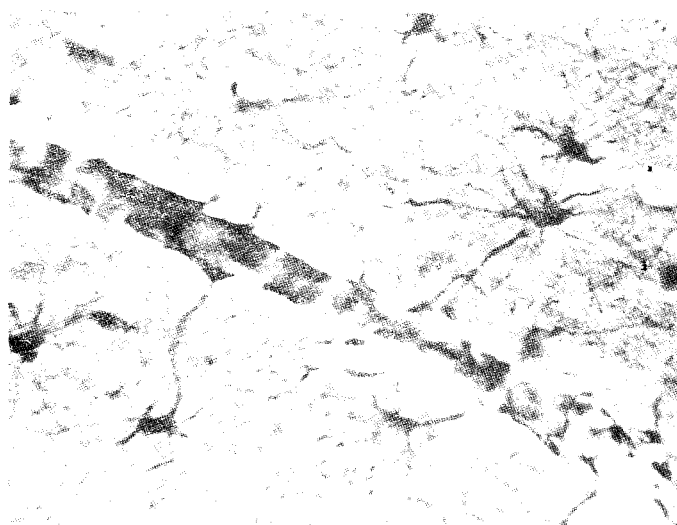
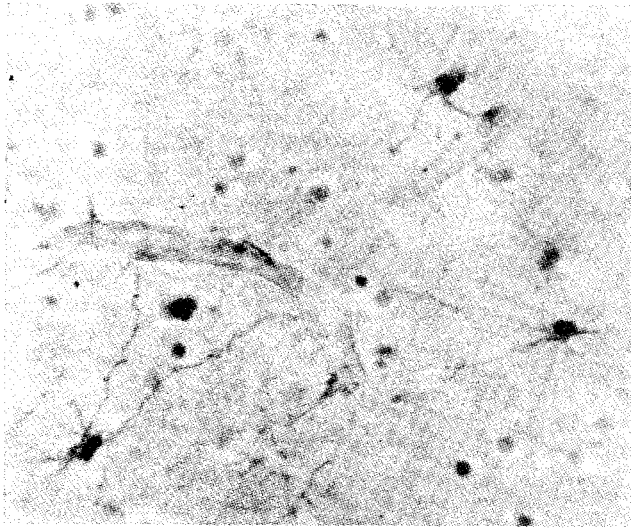


FIGURE 7

"Normal" looking astrocytes of the cerebral white matter in a case of subacute suffocation due to excessive blood aspiration. The severe hypoxia prior to death lasted for about one hour

presumed that in addition to the cortical contusion foci, changes in the astrocytes of the white matter and of the basal ganglia might be found that would fit Hallervorden's theory. However, apart from the grossly visible necroses, no acute swelling or degeneration in either the white matter or the brain stem was found histologically. The astrocytes had maintained their structure and in some places appeared to have shrunk, making it somewhat difficult to trace the cell processes over a short distance.



**FIGURE 8**

Astrocytes of the white matter in a case of subacute suffocation with especially fine processes showing tiny loops that look like knots.

### SUMMARY OF THE FINDINGS

In 50 cases of acute death a clasmatodendrosis of the astrocytes was found. Its pattern of distribution was essentially the same. The most severely affected part of every brain was the white matter of the cerebral hemispheres except for its immediate subcortical zone, the white matter of the cerebellum and the white areas of the lower brain stem. In most of the cases the cerebral cortex and the striate bodies showed a clasmatodendrosis also. However, the astrocytes of the first layer of the cortex, of the subependymal zone, of the subcortical area of the white matter, of the thalamus, hypothalamus, especially of the pallidum and the gray parts of pons and medulla oblongata, revealed in general merely a beginning clasmatodendrosis or no signs of degeneration at all.

When death followed a severe hypoxia lasting up to about 30 minutes, clasmatodendrosis usu-

ally was accompanied by acute swelling of the cells. This acute swelling usually failed to develop if death had occurred after a hypoxia of approximately 30 to 60 minutes' duration. In such cases the clasmatodendrosis was more or less confined to the white matter.

In 18 cases of subacute death with a minimum duration of about one hour, both the clasmatodendrosis and the acute swelling were absent. The cells had maintained their form although their size varied to some extent. Occasionally, they appeared so small as to suggest shrinkage.

In both groups, the span of time between death and fixation of the tissue varied from 7 to 48 hours. The rate of cooling of the bodies did not differ materially from that usually encountered in pathology.

For the development of the clasmatodendrosis, as well as for the conservation of the cell form, it is of interest that in 2 cases of acute suffocation in snow with comparatively fast cooling of the brain, clasmatodendrosis had developed; whereas in one case of subacute death, with fixation of the brain after 48 hours and the usual cooling of the body, the astrocytes even deep in the white matter did not show any sign of degeneration.

### DISCUSSION

Before going into detail, it may be stated that our hypothesis expressed in the beginning was obviously confirmed by these findings. Thus, figure 1 demonstrates the morphological effect of a rapid transition from the normal oxygen supply of tissue to its anoxic state side by side with a slow transition. Hence, not only the changes of the astrocytes within the focus, but also the conservation of the cells outside the focus constitute a positive finding.

In discussing the individual findings, the acute swelling will be discussed first. The question to be answered is whether it has developed within the very last moments of life or post mortem. The cases of instantaneous death suggest a postmortem development. To be sure, this conclusion was verified by animal experiments in collaboration with W. Noell. It was found that the swelling does not develop during the phase of hypoxia. It begins as soon as 10 to 15 minutes after death and may remain in the same state for one or more hours, depending on the temperature and on the cells involved.\*

\*A paper on these experiments will be published separately.

Therefore, it maybe considered as a sign of a beginning regressive process developing quickly under an anoxic condition due to an increase of intracellular fluid. It seems to be comparable to similar, early necrobiotic reactions of other cell types and may be reversible, as generally believed. Assuming, however, that for a very brief instant anoxia has not a deadly but a stimulative effect on the astrocytes, the acute swelling in its early stage could be considered as a progressive reaction which sets in abruptly, quasi an attempt of the living cell to overcome its abnormal situation. Indeed, the appearance is very similar to that of a hypertrophy of the astrocytes. It is, however, believed that there is no relationship between these two morphological manifestations. If the brain has been fixed very soon after death it may be very difficult to decide whether the alteration is a progressive or a regressive one, since vacuolization and a shaggy appearance of the dendrites may fail to develop. Differences in the structure of the nuclei are assumed to be of some significance. They are, however, not always distinct.

The second finding to be discussed is that of the clasmatodendrosis. Did this alteration develop intra vitam or post mortem? The cases of instantaneous death and the experience that in fresh softenings the necrobiotic reaction of the cells sets in after circulation has been arrested, suggest a postmortal development. The animal experiments verified this conclusion and revealed that at body temperature the first signs of generalized clasmatodendrosis in the deeper white matter can be noticed 30 to 60 minutes after death. Thus, we are dealing with the "postmortal" form of clasmatodendrosis which has been frequently discussed in the literature since the works of Eisath and Rosenthal.

Various attempts have been made to find criteria by which it would be possible to differentiate between the postmortal and intravital types of clasmatodendrosis. Walter has pointed out the possibility of utilizing its pattern of distribution, considering focal changes as suggestive of an intravital genesis and a generalized distribution of a postmortem development. Achucarro and Gayarre tried to achieve a differentiation on the basis of histological differences. They maintained the theory that in case of intravital degeneration the individual cell particles differ in size and are more or less detached from one another; whereas in postmortem degeneration the

cell particles are all dustlike and close together. However, Alzheimer, and later Spielmeyer, Jakob and others, stated that a histological differentiation of both forms is not possible. Rosenthal was of the opinion that such a differentiation is not even feasible because in both instances the clasmatodendrosis is a necrobiosis. His opinion must now be modified to allow for the fact that this holds true only if the circulatory system fails; hence the anoxia is acute. The fact that clasmatodendrosis developed in the cases of acute death herein reported with the same regularity as it does in embolic softenings can only be explained in this manner. In other words, after an acute death the brain is to be regarded as a very fresh "generalized softening." It differs from a localized softening inasmuch as the latter maintains body temperature and is still able to exchange some sort of fluid with its environment as long as the patient is alive. According to the author's experiments, lowering of the temperature causes a slowing down of the necrobiotic process only, but does not change it in principle. The absence of fluid exchange in such a generalized softening, likewise, does not seem to have any essential morphological effect in this very early stage of necrobiosis, as may be concluded from observations on larger and very fresh embolic softenings.

The causative factor of this process seems to be solely anoxia. The cases reported here indicate that a markedly increased or a decreased carbon dioxide content of the blood and the tissue has no obvious influence on either the acute swelling or the clasmatodendrosis. According to experience, however, there have been many cases of equally generalized clasmatodendrosis in patients who died of a severe affliction. The types of illnesses can be most diverse, ranging from senile dementia to severe toxic infections. Is it possible that in such cases some factor other than anoxia causes the clasmatodendrosis?

A number of such cases mentioned in the literature, obviously suffered an acute death. For instance, the first case of Alzheimer's investigations on ameboidosis of the glia concerned a catatonic who, without symptoms of any organic disorder, died suddenly. Struwe, Gruental, and Rothschild described similar cases and noticed in some of them the coincidence of clasmatodendrosis with acute death. The author investigated, in addition a number of his own cases of general

diseases, such as acute malaria tropica, uremic eclampsia, diabetic and hepatic coma, acute neosalvarsan poisoning, fatal burns, and septic conditions due to liver abscesses and other suppurative processes. Whenever he found a generalized clasmotodendrosis, the case history or interrogations as to the fatal issue revealed, in most cases, that death either was caused by acute failure of circulation or had occurred suddenly in a severe epileptic state; however if death was subacute, although toxically induced, no generalized clasmotodendrosis developed. In some of these cases the astrocytes did not indicate any trace of clasmotodendrosis even within a tissue infiltrate, as shown in figure 9. Such findings lead to the belief that generalized clasmotodendrosis, at least in the majority of toxic processes, is initiated not by toxins but by the acute mortal anoxia.

Next, consider the peculiar pattern of distribution of the clasmotodendrosis in the cases of acute death. Why is it always the white matter which is involved first and more markedly than the other regions of the brain? And, for instance, why are the subcortical astrocytes more resistant despite the fact that they belong to the white matter, too? One might think of a causative connection with the special vascular pattern of the

white matter (Cobb, Alexander, and Putnam). In this respect, the deeper parts of the white matter may be compared to the centers of the liver lobules in which vacuolization very often starts. Yet, the cases in which the circulation ceases abruptly everywhere at the same instant refute such a concept. One might further imagine that the cooling process in the outer layers of the brain would slow down the cell degeneration at an earlier time than in the inner layers. This assumption too is untenable; else the basal ganglia, because of their central position, would have to be affected most severely by degeneration. Many other possible explanations have been considered and it has been concluded that the variations in the rate of the cellular degenerative process point to differences in the normal metabolism of the cells in accordance with the different functions of various portions of the brain.

The fact that the astrocytes retained their structure whenever the premortal hypoxic phase lasted longer than about one hour is obviously the most striking finding in this investigation. As mentioned before, this means that the conservation of the cell structure is significant and must be considered as a specific, or to be more accurate, as a pathological finding in itself. On account of the homogeneousness of cell structure in healthy material treated by the same methods, it has been commonly assumed that such cell structures are equivalent to those of normal living cells (*Aequivalentbild* of Nissl). This conclusion is based upon the presupposition that in so-called normal autopsy material the cells do not change their structure, at least not during the usual span of time between death and fixation. But, based on the reported findings, this holds true only for subacute death. Consequently, the cells are not equivalent to normal living ones but to those which lived under the strain of severe subacute hypoxia. In this way it is conceivable that in the subacute cases the size of the astrocytes showed some variation. There seems to be but one possibility to obtain a true equivalent picture; namely, by fixing the tissue at the moment of instantaneous death. Since this cannot be performed in human pathology, an equivalent picture in a strict sense does not exist. It is actually a necrobiosis of the cells, which is characterized by preservation of the cell structure.

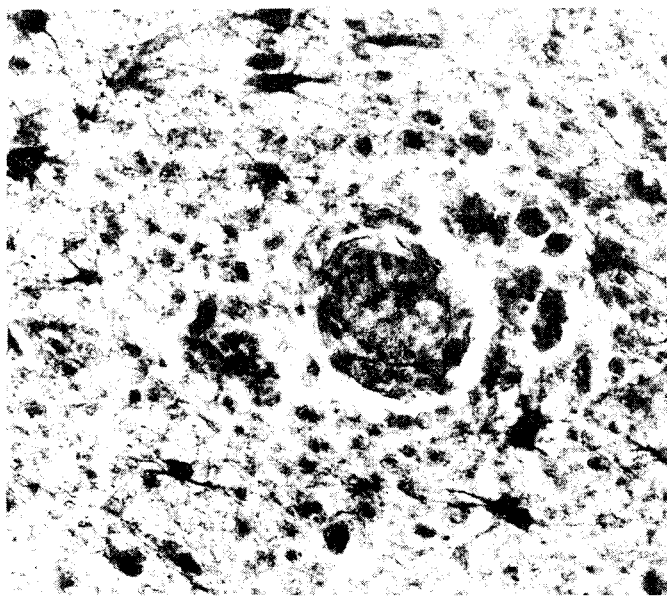


FIGURE 9

Astrocytes within a tissue infiltrate in a case of an acute encephalomyelitis. No trace of clasmotodendrosis.

This raises the problem of differentiating these two types of necrobiosis by a proper nomenclature. Since both types are caused by the anoxia of death, we may call them *mortally induced necrobioses*, or more briefly, *mortal necrobioses*. The cell destruction might be described by the term *morphotropic*, the preservation of the cell form, by *morphostatic*. Consequently, the terms *morphotropic mortal necrobiosis* and *morphostatic mortal necrobiosis* are proposed. Naturally, the latter proves to be correct only for a certain period of time after death, since the cell form will disintegrate eventually. This period, however, seems to be long enough for the purposes of practical histopathology. In one additional case of subacute death the astrocytes were still intact 7 days after death, as shown in figure 10; the corpse had been kept in a cool place.

The difference in the morphological behavior of the cells, must be considered as a reflection of a difference in their biochemical make-up and behavior after entering the state of anoxia. Without mentioning details in this obviously intricate matter it may be assumed that at the moment of sudden death (decapitation) the cells are fully supplied with everything essential for their normal function. Then, while oxygen is lacking, a continuous breakdown of their energy material

occurs. Since there is no blood circulation the catabolic products will accumulate within and around the cells progressively influencing their structural elements. Acute swelling, vacuolization, and clasmatodendrosis are the corresponding morphological reactions. However, in death preceded by a severe hypoxia the energy material of the cells will be reduced under the strain. Most of the reduction products will be removed by the still-functioning circulation. The usual metabolic pattern may even change. Regardless of what may occur in detail, the over-all biochemical condition of the cells at the beginning of the anoxia will be different from their condition in case of sudden death. Histologically one can expect a different morphological reaction of the cells. It is believed that the failure of the acute swelling and of the clasmatodendrosis as well as the variation in size of the intact cells are to be considered as morphological effects of such metabolic alterations.

These findings are apparently not confined to the astrocytes alone. They apply also to the ganglion cells as will be discussed in a separate paper (see Report No. 1). As far as the cells in the other organs are concerned, it is believed that a similar rule may be applied, since in case of an infarct they likewise show necrotic and "normal" tissue side by side.

### SUMMARY

A 5-hour-old embolic softening in the brain led to the theory that the picture of clasmatodendrosis of the astrocytes in the focus, and of the "normal" structure of the astrocytes in the surrounding areas, must be attributed to the fact that in the focus an acute transition, and in its vicinity a subacute transition, from the normal oxygen supply to anoxia had taken place. Since it was assumed that, as far as the tissue is concerned, the standstill of the entire circulation when death occurs is principally equivalent to a local disturbance of the circulation, this problem has been investigated in groups of acute and of subacute cases of death.

This investigation showed that in all cases of acute death, in which the brain had been fixed 8 to 46 hours after death, a clasmatodendrosis of the astrocytes had occurred. If death was preceded by a phase of severe hypoxia not exceeding about 30 minutes, the clasmatodendrosis was usually accompanied by an acute swelling.

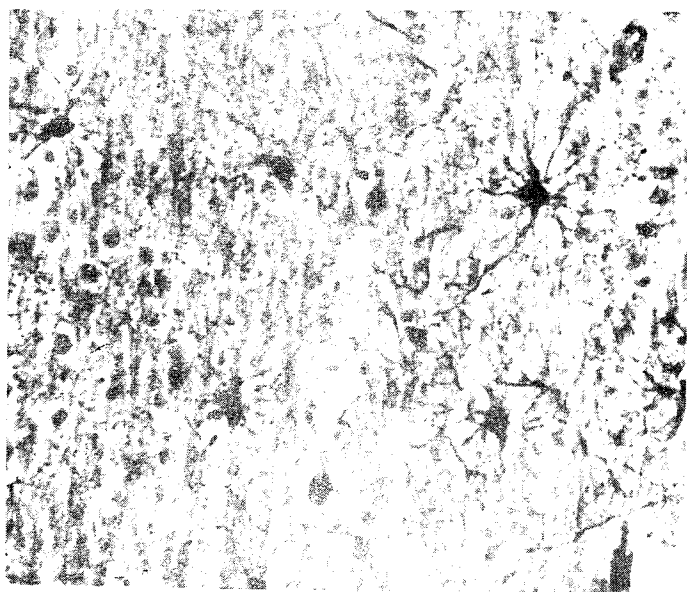


FIGURE 10

Astrocytes of the white matter in a case of subacute death (gas embolism) fixed 7 days after death.

If the hypoxic phase lasted about 30 to 60 minutes, there were generally no indications of an acute swelling.

In cases of subacute death preceded by a phase of severe hypoxia lasting not less than 60 minutes, the astrocytes revealed a certain variation in size and sometimes a peculiar curling of their dendrites. Clasmotodendrosis, however, was missing, even if the fixation of the brain was carried out 48 hours and more after death.

The cell changes found after acute death are principally the same as those after a fresh, local

disturbance of the circulation caused by an embolism. They constitute a regular phenomenon. Consequently, after acute death the brain has to be considered as in a state of generalized softening.

As far as the preservation of the cell structure is concerned, it is also a characteristic and positive finding since it can be observed in cases of subacute death only.

The importance of these investigations in relation to certain problems of neuropathology is discussed.

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USAF School of Aviation Medicine, Project No. 21-23-004, Report No. 2  
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